

**REMARKS**

Claims 1-8, 16 and 29-29 are presently pending and under consideration.

**Regarding 35 U.S.C. § 112, First Paragraph (Written Description)**

Applicants respectfully traverse the rejection of claims 1-8, 16, 28 and 29 under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, had possession of the claimed invention at the time the application was filed.

The Examiner concedes that original claims 1 and 10 have support for an antibody binding to SEQ ID NO: 68, and modulating the biological activity of a malignant cell that express a frizzled 5 receptor. However, the Examiner appears to assert that the specification as originally filed does not have support for the antibody the antibody that binds to the amino terminal of SEQ ID NO: 68 as inhibiting growth of the malignant cell or being effective for immunotherapy of a malignant cell that overexpresses the frizzled 5 receptor.

Claim 1 is directed to a purified antibody that binds a frizzled 5 receptor, wherein the antibody specifically binds to at least one epitope in an amino terminal extracellular domain of the frizzled 5 receptor expressed on a malignant cell, wherein the amino terminal extracellular domain is SEQ ID NO:68, and wherein the antibody inhibits growth of the malignant cell that expresses the frizzled 5 receptor. Claim 28 is identical to claim 1, except that the is recited as effective for immunotherapy of a malignant cell that overexpresses the frizzled 5 receptor.

Originally filed claim 10 encompasses a purified antibody for modulating the biological activity of a malignant cell that expresses a frizzled receptor, wherein the antibody binds to at least one epitope in an extracellular domain of the frizzled receptor expressed on the malignant cell, wherein the extracellular domain has a sequence that is greater than 80% homologous to SEQ ID NO: 68. The specification, at page 22, lines 306, explicitly defines the claim phrase **"modulating a biological activity of a malignant cell"** to include, *inter alia*, as **cell growth inhibition (Claim 1)** or the **ability to elicit a cytotoxic response (Claim 28)** to the malignant cell. The specification thus provides explicit written description for the subject matter of claims

1-8, 16, 28 and 29 and removal of the rejection under 35 U.S.C. §112, first paragraph, for allegedly containing new matter is respectfully requested.

**Regarding 35 U.S.C. § 103**

Applicants respectfully traverse the rejection of claims 1-8, 16 and 28-29 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Tanaka et al., *Proc. Natl. Acad. Sci. USA* 95:10164-10169 (1998) in view of U.S. Patent No. 5,677,171 (Hudziak et al.).

Applicants respectfully point out that there are at least two deficiencies with regard to the aforementioned rejection: (1) the cited references provide no motivation to modify their combined teachings with a reasonable expectation of success with regard to pursuing frizzled 5 as a target for inhibition of malignant cell growth or immunotherapy, and (2) the primary reference teaches away from the claimed invention.

The claims are directed to antibodies that bind to at least one epitope in an amino terminal extracellular domain of the frizzled 5 receptor expressed on a malignant cell, wherein the amino terminal extracellular domain corresponds to SEQ ID NO:68, wherein the antibody inhibits growth of the malignant cell that expresses the frizzled 5 receptor or wherein the antibody is effective for immunotherapy of a malignant cell that overexpresses the frizzled 5 receptor. Related pharmaceutical compositions to the former are also claimed.

A claimed invention is unobvious when it represents more than “the predictable use of prior art elements according to their established functions.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. \_\_\_, 127 S.Ct. 1727, 1740 (2007). As explained in detail below, the targeting of frizzled 5 receptor with an antibody to inhibit growth of a malignant cell that expresses the frizzled 5 receptor or to effect immunotherapy of such a malignant cell according to the pending claims is far from a predictable use of prior art elements described in the cited references according to their established functions.

Tanaka et al. disclose expression of seven frizzled genes in esophageal carcinoma compared to adjacent normal mucosa. Based on the human esophageal carcinoma-specific expression pattern observed *only* with FzE3, Tanaka al. speculate that FzE3 may be a key molecule in the pathogenesis of human esophageal carcinomas. Despite the findings of strong differential expression as observed *only* with FzE3, the authors still concede that additional

analysis is warranted to confirm their speculation (page 10169). Far from suggesting a role for the frizzled 5 receptor in the pathogenesis of human esophageal carcinomas, the authors make no mention of frizzled 5 other than showing its non-differential expression pattern Figure 1B. In sum, the frizzled 5 receptor lacks the differential expression in human esophageal carcinomas that was observed with FzdE3 and that led Tanaka et al. to conclude a potential role for FzdE3 in the pathogenesis of the condition. Therefore, targeting the frizzled 5 receptor would not have been considered a potential target and one of ordinary skill in the art would not have pursued the claimed invention with any expectation of success. As discussed in the following paragraph, viewing Tanaka et al. in combination with Hudziak et al., does not strengthen the case for obviousness.

The deficiencies of the primary reference are not cured by Hudziak et al., which is directed entirely to the application of antibodies to target receptors for growth factors that are known to stimulate tumor cell growth and division. See, for example, C5:29-38; C6:21-25. Significantly, neither Hudziak et al. nor Tanaka et al. disclose that frizzled 5 is a growth factor receptor or characterize frizzled 5 ligands as growth factors. Even more importantly, Tanaka et al. concedes that the role of individual members of the frizzled family, which includes frizzled 5, in cancer has not been explored:

More recently, the **Frizzled (Fz) family** of seven-transmembrane proteins have been shown to act as receptors for Wnt proteins and therefore may be involved in cell migration patterns. However, **the role of specific member(s) of this gene family in human tumor development and metastasis has not yet been explored.**

Tanaka et al., page 10164, left column (Emphases supplied; citations omitted). It is respectfully submitted that it is unclear how the skilled person would be at all motivated to combine the two references with any expectation of success when Hudziak et al. effectively describes conditions for producing antibodies that are based on known tumor enhancing growth factor activities of the targets and that were not met by the frizzled 5 receptor described in passing by Tanaka et al., where it is described as having no implication in cancer.

A reference may be the to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.” *In re Gurley*, 27 F.3d 551,

553 (Fed. Cir. 1994); *see KSR*, 127 S. Ct. at 1739–40 (explaining that when the prior art teaches away from a combination, that combination is more likely to be nonobvious). It is respectfully submitted that Tanaka et al. teaches away from the claimed invention by showing that the frizzled 5 receptor lacks the differential expression in human esophageal carcinomas that was observed with FzdE3 and by proposing a potential role for FzdE3 in the pathogenesis of the condition without making a similar prediction with regard to frizzled 5. The silence of Tanaka et al. on frizzled 5 is compounded by the author's admission that the role of frizzled 5 in cancer was unexplored (see citation above). Therefore, Tanaka et al. effectively discourages targeting the frizzled 5 receptor and represents a teaching away from the claimed invention.

In view of the above, Applicants respectfully request removal of claims 1-8, 16 and 28-29 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Tanaka et al., *Proc. Natl. Acad. Sci. USA* 95:10164-10169 (1998) in view of U.S. Patent No. 5,677,171.

### **CONCLUSION**

In light of the remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned attorney if there are any questions or if it is believed that a telephonic interview may expedite prosecution.

09/847,102

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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